(12) UK Patent Application (19) GB (11) 2 167 665 A

(43) Application published 4 Jun 1986

(21) Application No 8430598

(22) Date of filing 4 Dec 1984

(51) INT CL[4]
A61F 2/00 A61M 25/00

(52) Domestic classification (Edition H):
A5R CG

(56) Documents cited
GB 1602163 GB 1205770

(58) Field of search.
A5R
Selected US specifications from IPC sub-classes A61F A61M

(71) Applicant
The University of Liverpool (United Kingdom), Senate House, Abercromby Square, P O Box 147, Liverpool L69 3BX

(72) Inventor
Clement Henry Bamford

(74) Agent and/or Address for Service
Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA

(54) **Platelet aggregation inhibitor for use in polymeric surgical devices**

(57) A polymeric surgical device such as a suture, ligating clip, catheter or artificial artery, has a platelet aggregation inhibitor, such as 5-(6-carboxyhexyl-1-(3-cyclohexyl-3-hydroxypropyl) hydantoin, associated therewith. The inhibitor may be coated onto the device or incorporated into the polymer.

GB 2 167 665 A

SPECIFICATION

Improvements in polymeric surgical devices

The present invention relates to improvements in polymeric surgical devices for use in blood vessels in the body, such as sutures, ligating clips, catheters, and internal prostheses.

Sutures and ligating clips are widely used in surgical procedures such as cardiac or vascular surgery, for instance to close off or connect together blood vessels or to connect internal prosthetic devices such as artificial arteries into an existing artery in place of an excised segment thereof.

Catheters are also often placed in blood vessels, for instance for monitoring blood pressure or composition or for extracting blood for analysis or renal dialysis.

However, the use of such devices in blood vessels may lead to the formation of blood clots around the device. For instance, it has been shown that in artificial arteries in the form of heat crimped, seamless, woven tubes of DACRON or TEFLON there is a tendency for blood clotting to take place on the internal surface of the tube in the region of the sutures if the tube's internal diameter is less than about 7mm.

According to the present invention a polymeric surgical device is provided having associated therewith a platelet aggregation inhibitor (PAI).

An example of a suitable PAI is the prostaglandin analogue 5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl) hydantoin.

The polymeric device may be made from a natural or artificial polymer which may be absorbable or non-absorbable.

Suitable non-absorbable polymers are polypropylene, polyethylene, nylon or, for sutures, silk. Suitable absorbable polymers are polyglycolide, polylactide or polydioxanone.

The PAI may be associated with the polymeric device by, for instance,

(i) coating the device with a size containing the PAI,

(ii) chemically combining the PAI with the polymer, or

(iii) incorporating the PAI in the device during manufacture of the device.

In method (i) the PAI may simply be dissolved or mechanically dispersed in a size polymer solution. The solution is then applied to the device as a size. The size polymer may be, for instance, a styrene/maleic anhydride copolymer. In use, the PAI will diffuse out of the size polymer coating or matrix and so confer platelet aggregation inhibiting properties on the device.

The rate of such diffusion will depend on the molecular constitutions of the PAI and the size polymer matrix, and in some cases it may be undesirably high. In this event, the platelet aggregation inhibiting properties will be lost too rapidly. Thus it may be necessary to attach the PAI to the size polymer chain by chemical bonds. Such a platelet aggregation inhibiting polymer (PAIP) may be used as a component of the size for coating the device as described above. The reduced rate of diffusion of the PAI bonded to the bulky size polymer chain would ensure a longer period of platelet aggregation inhibiting activity of the device.

In method (ii), chemical attachment of the PAI to the polymer of the device represents the extreme degree of immobilisation of the PAI. This method ensures that the surface of the device presented to the blood stream is covered to a significant extent by bound PAI molecules.

The PAI may be attached to the polymer either "permanently", that is by chemical bonds which are not broken by the action of enzymes or other factors in blood, or "releasably", that is by chemical bonds which can be broken by the action of the enzymes or other factors in blood. In the first case, the platelet aggregation inhibiting activity is essentially a surface effect. In the second case there is a release of PAI from the surface and, more slowly, from the underlying layers of the device. The release of the PAI substantially inhibits thrombus formation on and in the neighbourhood of the device.

In method (iii) the PAI may be mechanically incorporated into the device either as itself or as a PAIP. For instance a polymer solution containing the PAI or a PAIP may be spun to produce a suture fibre or cast to produce a ligating clip or catheter. Preferably such spinning or casting is carried out at a temperature not significantly higher than ambient temperature.

A device according to the invention can only be produced by spinning or moulding a polymer melt containing the PAI or a PAIP if the PAI is thermally stable. However melt spinning or melt moulding may be used to form a device without any PAI therein. The PAI may then be incorporated in the device by immersing it in a solution containing a swelling agent and the PAI. This procedure is particularly suitable for producing nylon or polypropylene sutures and can be carried out before the final stretching process in suture fibre manufacture.

The details of the processes used in methods (i) and (ii) to chemically bond the PAI to the polymer or size polymer clearly depend on the chemical structures of the PAI and the polymer of which the device or the size is composed. If appropriate functional groups are present on the polymer and if complementary functional groups which can be used without impairing its activity are present on the PAI, any conventional linking type of reaction such as esterification, etherification or amide formation can be used.

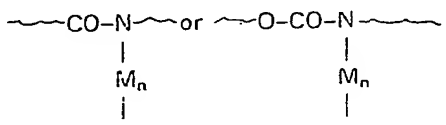
Alternatively, a polymerisable double bond may be introduced into the PAI molecule. The modified PAI molecule may be copolymerised with a vinyl monomer to produce a PAIP. The modified PAI molecule or the PAIP may be grafted into the polymer from which the device is made, or the PAIP may be used in method (i) or method (iii) above. For instance, the prostaglandin analogue 5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-

hydroxypropyl) hydantoin may be esterified with a vinyl monomer such as N-vinylpyrrolidone or, preferably, 2-hydroxyethylmethacrylate.

One particular method for grafting such a modified PAI onto a polymer embodying amide (or peptide) or urethane groups (for instance nylon, protein or polyurethane polymers) involves subjecting the polymer to a mild halogenation procedure, for instance using sodium hypochlorite or hypobromite. This treatment converts some of the –NHCO– or –NHCOO– groups into –NXCO– or –NXCOO– groups (wherein X is chlorine or bromine).

The resulting halogenated polymer is dissolved in a vinyl polymer (M) and reacted with a free radical producing agent to produce free radicals –ṄCO– or –ṄCOO– or the polymer. The free radical producing agent may be, for instance, a transition metal carbonyl such as $Mo(CO)_6$, which is reacted thermally at about 60°C to form the free radicals, or $Mn_2(CO)_{10}$, which is reacted photochemically at a wavelength of 436nm to form the free radicals.

Polymerisation of the free-radical containing polymer with the monomer M yields a graft copolymer containing structures such as



If the vinyl monomer M contains a proportion of modified PAI molecules, the grafted M_n chains will include units having the PAI molecule attached thereto.

It is envisaged that the present invention will be of particular, but not exclusive, application to surgical sutures for suturing blood vessels in cardiac and vascular surgery to substantially inhibit spontaneous thrombus formation.

It is also envisaged that any polymeric surgical device, in particular those for use in or adjacent blood vessels, can be provided with PAI according to the present invention. For instance, it is believed that the present invention is applicable to ligating clips, catheters and artificial arteries, as long as they are made of polymeric material.

One embodiment of a device according to the invention is now described by way of example only.

Two catheters of 2mm bore were prepared and placed in the main vein of a dog. The first was a polystyrene coated catheter; the second was coated with polystyrene in which 5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl) hydantoin had been dispersed. Both catheters remained in flowing blood for four hours and then each was withdrawn. The untreated catheter was found to be covered in thrombus material whereas that which was coated with the platelet aggregation inhibitor was not.

CLAIMS

1. A polymeric surgical device having associated therewith a platelet aggregation inhibitor.
2. The device of Claim 1 wherein the platelet aggregation inhibitor is 5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl) hydantoin.
3. The device of Claim 1 or Claim 2, which is made from a non-absorbable polymer.
4. The device of Claim 3, wherein the non-absorbable polymer is polypropylene, polyethylene, nylon or silk.
5. The device of Claim 1 or Claim 2, which is made from an absorbable polymer.
6. The device of Claim 5, wherein the absorbable polymer is polylactide, polyglycolide or polydioxanone.
7. The device of any one of Claims 1 to 6 in the form of a suture.
8. The device of any one of Claims 1 to 6 in the form of a ligating clip, catheter or artificial artery.
9. A method of producing a device according to any one of Claims 1 to 8, comprising coating the device with a size containing the platelet aggregation inhibitor.
10. The method of Claim 9, wherein the size contains a size polymer.
11. The method of Claim 10, wherein the platelet aggregation inhibitor is chemically bonded to the size polymer.
12. A method of producing a device according to any one of Claims 1 to 8, comprising chemically combining the platelet aggregation inhibitor with the polymer of which the device is composed.
13. A method of producing a device according to any one of Claims 1 to 8, comprising incorporating the platelet aggregation inhibitor in the polymer of which the device is composed.
14. The method of Claim 13, wherein the device is spun or cast from a solution containing the platelet aggregation inhibitor.
15. The method of Claim 14, wherein the solution contains a polymer to which the platelet aggregation inhibitor is chemically bonded.
16. The method of Claim 13, wherein the device is immersed in a solution containing a swelling agent and the platelet aggregation inhibitor.
17. The method of any one of Claims 11, 12 and 15, wherein the platelet aggregation inhibitor is chemically bonded to the polymer by esterification, etherification or amide formation.

18. The method of any one of Claims 11, 12 and 15, wherein the polymer contains amide or urethane groups, the platelet aggregation inhibitor is attached to a monomer containing a polymerisable double bond, a free radical is produced on a plurality of the amide or urethane groups, and the inhibitor containing monomer, optionally in admixture with unmodified monomer, is free-radical graft polymerised onto the polymer.

Printed in the UK for HMSO, D8818935, 4/86, 7102.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.